The Sri Lankan Twin Registry: 2012 Update

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The Sri Lankan Twin Registry (SLTR), established in 1997, is a unique resource for twin and genetic research in a low- and middle-income country (LMIC). It comprises of a volunteer cohort of 14,120 twins (7,060 pairs) and 119 sets of triplets, and a population-based cohort of 19,040 (9,520 pairs) twins and 89 sets of triplets. Several studies have been conducted using this registry, including the Colombo Twin and Singleton Study (CoTaSS 1; 4,387 twins, 2,311 singletons), which have explored the prevalence and heritability of a range of psychiatric disorders as well as gene-environmental interplay. Currently, a follow-up study (CoTaSS 2) of the same cohort is underway, looking at the prevalence and interrelationship of key cardiovascular and metabolic risk markers (e.g., metabolic syndrome). A significant feature of CoTaSS 2 is the establishment of a biobank. Current SLTR work is extending beyond mental health and the interface between mental and physical health to new horizons, extending collaborations with the wider global twin research community. Ethics and governance have been given special emphasis in the initiative. Capacity building and public engagement are two crucial components. Establishment of a state-of-the-art genetic laboratory was a major accomplishment. SLTR is a classic showcase of successful North–South partnership in building a progressive research infrastructure in a LMIC.

Keywords: twin research, Sri Lanka, developing world, North-South collaboration, gene-environment interaction

Twin studies allow us to determine the degree to which traits and disorders are heritable within specific populations. Most of these studies use volunteer registries of twins, and most are in North America, Europe, and Australia (Boomsma et al., 2002). However, it is not known how far these findings are generalizable and applicable to developing countries, and application of twin study methods for cross-cultural comparisons is limited. Population-based registries are rare, even in the West (Boomsma et al., 2002). The uniqueness of the Sri Lankan Twin Registry (SLTR) lies in the fact of it being the first in the developing world (Sumathipala et al., 2000a, 2002). It is still one of the few large-scale, functioning population-based registries in the developing world (Van Dongen et al., 2012).

Brief History of SLTR

The development of a twin registry in Sri Lanka was proposed and initiated by AS in 1997 (Sumathipala et al., 2002). The objective was to establish a nation-wide twin registry, starting initially as a volunteer registry, and subsequent development of a population-based registry. It was envisaged that it would become a platform for a multidisciplinary approach toward twin research in the low- and middle-income country (LMIC) context. The evolutionary process of the SLTR has been reported previously (Siribaddana et al., 2006; Sumathipala et al., 2000a, 2002). Several strategies for twin recruitment were employed; initial enrolling of volunteer twins through media campaigns was followed by tracing of twins through birth...
TABLE 1
Age Group Description of Volunteer Twin Cohort

<table>
<thead>
<tr>
<th>Age group</th>
<th>Male–male</th>
<th>Female–female</th>
<th>Male–female</th>
<th>Missing</th>
<th>Total pairs</th>
</tr>
</thead>
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<tr>
<td>Below 10</td>
<td>161</td>
<td>189</td>
<td>109</td>
<td>0</td>
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</tr>
<tr>
<td>11–20</td>
<td>899</td>
<td>1,032</td>
<td>642</td>
<td>6</td>
<td>2,579</td>
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<tr>
<td>21–30</td>
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<td>867</td>
<td>449</td>
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<td>2,057</td>
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<tr>
<td>41–50</td>
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<td>197</td>
<td>134</td>
<td>5</td>
<td>498</td>
</tr>
<tr>
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<td>59</td>
<td>77</td>
<td>73</td>
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<td>212</td>
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<tr>
<td>61–70</td>
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<td>47</td>
<td>25</td>
<td>0</td>
<td>105</td>
</tr>
<tr>
<td>71–80</td>
<td>10</td>
<td>15</td>
<td>13</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Above 81</td>
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<td>4</td>
<td>4</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Age not known</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>05</td>
</tr>
<tr>
<td></td>
<td>2,386</td>
<td>2,919</td>
<td>1,728</td>
<td>27</td>
<td>7,060</td>
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</tbody>
</table>

TABLE 2
Age Group Description of Population-Based Twin Cohort

<table>
<thead>
<tr>
<th>Age group</th>
<th>Male–male</th>
<th>Female–female</th>
<th>Male–female</th>
<th>Missing</th>
<th>Total pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 10</td>
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<td>249</td>
<td>204</td>
<td>34</td>
<td>777</td>
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<tr>
<td>11–20</td>
<td>689</td>
<td>749</td>
<td>466</td>
<td>60</td>
<td>1,996</td>
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<tr>
<td>21–30</td>
<td>612</td>
<td>637</td>
<td>441</td>
<td>83</td>
<td>1,773</td>
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<tr>
<td>31–40</td>
<td>571</td>
<td>647</td>
<td>508</td>
<td>110</td>
<td>1,836</td>
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<tr>
<td>41–50</td>
<td>451</td>
<td>468</td>
<td>415</td>
<td>146</td>
<td>1,480</td>
</tr>
<tr>
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<td>297</td>
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<td>118</td>
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<td>118</td>
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<td>128</td>
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<td>475</td>
</tr>
<tr>
<td>71–80</td>
<td>36</td>
<td>65</td>
<td>45</td>
<td>46</td>
<td>192</td>
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<tr>
<td>81+</td>
<td>22</td>
<td>18</td>
<td>05</td>
<td>19</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>3,052</td>
<td>3,282</td>
<td>2,488</td>
<td>698</td>
<td>9,520</td>
</tr>
</tbody>
</table>

The SLTR is a sustainable program, established through a strategic, multidisciplinary partnership between the Institute for Research and Development (IRD) and Institute of Psychiatry, King’s College London. This initiative was mainly built upon competitive and substantial funding from the Wellcome Trust.

Current Status of the SLTR

Volunteer Cohort

This was established by recruiting twins through a national newspaper advertising campaign, as an island-wide registry. The SLTR volunteer cohort has 14,120 twins (7,060 pairs) and 119 sets of triplets registered. The age range is from 1 to 85 years. However, 72% of twins are less than 30 years of age. It comprises of 2,386 male–male, 2,919 female–female, and 1,728 male–female twin pairs. Gender details are not available for 27 twin pairs. Triplets comprise of 23 all male sets, 36 all female sets, and 59 mixed gender sets. Details are missing for 1 set. Zygosity identification has not been carried out for the volunteer cohort. Further details of gender and age groups are given in Table 1.

Population-Based Cohort

This is confined only to the Colombo district. The SLTR population-based cohort has 19,040 twins (9,520 pairs) and 89 sets of triplets registered. The age ranges from 6 to 96. Twins comprise of 3,052 male–male, 3,282 female–female, and 2,488 male–female pairs. Gender details are missing in 698 pairs. Triplets comprise 25 sets of all males, 39 sets of all females, and the rest of mixed gender. Further details on gender and age groups are also given in the Table 2. Zygosity was ascertained only on twins who participated in the Colombo Twin and Singleton Study (CoTaSS 1). There were 2,274 dizygotic pairs and 1,691 monozygotic pairs; information was missing for 30 (total 3,995). Details are given in Table 3. The overlap between the island-wide volunteer cohort and population-based Colombo district cohort is 334 twins.

Zygosity Assessment

Translation, adaptation, and preliminary validation of a zygosity determination questionnaire by Ooki et al. (1993) were undertaken at the outset (Sumathipala et al., 2000b). However, this questionnaire was not validated against the
studies in western countries for depression, fatigue, and tobacco use (Ball et al., 2009, 2010c; Zavos et al., 2012). However, some differences were noted. For example, the heritability of a broad depression diagnosis was found to be significantly lower in men compared to women in this population, and this heritability was lower than most studies in Europe, Australia, and North America (Ball et al., 2009).

### Gene-Environment Interplay

We investigated a range of environmental exposures and their genetic or environmental contribution to depression and fatigue (Ball et al., 2010a). Gene-environment correlation was evident for some of the measured environments. Early school leaving and standard of living showed environmentally mediated effects on depression in men. In women, life events were associated with depression partly through genetic pathways. For fatigue, there were environmentally mediated effects and strong suggestions of family-environmental influences.

Involving a parallel singleton sample allowed us to report current and lifetime prevalence rates of psychiatric disorders in Sri Lanka. Comparison with the twin sample suggested that prevalence rates in twins were representative of the wider population, once adjusted for factors such as age (Ball et al., 2010a, 2010b; Zavos et al., 2012).

### CoTaSS Follow-Up Study (CoTaSS 2)

Previous research has provided evidence of an association between cardiovascular disease, diabetes, and depression (Katon et al., 2005). In the CoTaSS 2, we are exploring the prevalence and interrelationship of a number of key cardiovascular and metabolic risk markers (e.g., metabolic syndrome). Diabetes, heart disease, and depression have become significant public health priorities in Sri Lanka. Therefore, an investigation into the extent of overlapping genetic and environmental influences is a timely requirement.

The main aims of the CoTaSS 2 are: (1) estimating the prevalence of the component phenotypes which make up ‘metabolic syndrome’ in Sri Lanka; (2) investigating the genetic architecture of metabolic syndrome phenotypes, and estimate the extent to which phenotypic correlations are explained by shared genetic or environmental effects; (3) determining whether there is a significant etiological overlap between depression and the component phenotypes of metabolic syndrome.

The CoTaSS 2 study was initiated in May 2012, 5 years after the completion of the CoTaSS 1 study data collection. We have successfully managed to trace around 1,600 twins of baseline sample, and have completed 1,336 questionnaire interviews by mid-October 2012. The response rate is around 83%. Collection of biological material (blood) was started at a later stage and is currently in progress. Table 4 presents a summary comparison of CoTaSS 1 and 2 study attributes.
A sub-study within the CoTaSS 2 phase aims to evaluate the contribution of sleep and activity levels to the prevalence of metabolic syndrome and depression in Sri Lanka, using self-report and actigraphy. It is led by NG and will be the first study to determine population-based estimates of validated sleep parameters in a developing country (Stranges et al., 2012).

**Major Goals of the SLTR**

We look to extend our current work beyond mental health, and interface between mental and physical health. Through the CoTaSS 2, we have obtained the necessary ethical clearance for biobanking DNA and serum/plasma. We intend to engage in epigenetic, genome-wide association, and candidate gene studies. Through these studies, we are looking to expand our horizons and extend our collaboration with the wider global twin research community. We look forward to working with the international twin research community in twin data harmonization. Gradual expansion of the existing Colombo-based registry to rest of the country is also being targeted.

Since inception, our strategic agenda has been to work toward a sustainable center of excellence in twin and genetic research in a LMIC through North–South collaboration. We thereby aim to expand the twin research program through multidisciplinary and cross-disciplinary approaches. Capacity building in relevant expertise is an integral part in our initiative.

In keeping with one of our primary targets set at the inception of SLTR, we have established a state-of-the-art genetic laboratory.

**Ethics and Governance**

The SLTR has huge potential as a unique resource due to its location, size, and design. However, as it is from a resource-poor country it could be vulnerable to exploitation for easy and cheap research. In order to protect the SLTR and its registrants, we followed carefully designed ethical and governance frameworks, which have been developed in parallel to SLTR (Sumathipala et al., 2002).

Initially, ethical clearance was obtained from ethics committees at the Faculty of Medicine, University of Colombo and the Institute of Psychiatry, London (Sumathipala et al., 2000a). For the CoTASS 1 study, ethical clearance was obtained from the Institute of Psychiatry, London, Sri Jayewardenepura University Ethics Committee, Sri Lanka, and also from the WHO’s Ethics Committee (Siribaddana et al., 2006). For the CoTaSS follow-up study and the biobank, ethical clearance was obtained from the Institute of Psychiatry, London, and the Sri Jayewardenepura University Ethics committee.
Specific National and Regional Issues
Cultural attitudes toward twins have not been specifically studied in Sri Lanka. Even though not systematically investigated or documented, there is indirect evidence of a negative attitude toward genetic research in Sri Lanka. There have been a few media reports on exporting genetic material, portrayed as an exploitation of Sri Lankan genetic heritage. Therefore, since the beginning of the SLTR, being sensitive to cultural and social challenges has been our credo. To this end, establishing the genetic lab was a major strategic accomplishment.

Public Engagement
Public engagements have been one of the core themes running through all of the work conducted at the IRD, which houses the twin registry as one of its main research programs. SLTR public engagement work includes publishing regular newsletters for twins, using the IRD trilingual journal to create awareness about twin research among the public, and a Wellcome Trust-funded 3-year project (Multiples Engage in Research through Culture — MERC) led by SS and AS.

Discussion
Scarcity of research capacity in LMIC has been well established (Patel, 2007; Razzouk et al., 2010; Siriwardhana et al., 2011). However, the SLTR and the wider IRD initiative have showcased how successful North–South partnerships can overcome barriers to minimize the 10/90 divide (where 90% of global research funding targets the disease burden of only 10% of world population; Siriwardhana et al., 2011). This is especially poignant considering the facts that twin research concept was novel to Sri Lankans, the existing scarcity of research funding and lack of local expertise in twin method. However, in a perfect example of North–South collaboration, support and expertise came from colleagues at King’s College London to establish SLTR and ensure its sustenance.

Author Contributions
Authorships are given in descending order of seniority with the SLTR starting with AS.

Acknowledgments
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We would further like to acknowledge the IRD executive committee, other staff, and research assistants.

References


